PHYSIOLOGICAL EFFECTS OF HAEMORRHAGE

by

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BLOOD VOLUME IS defined as the sum of the volume of cells and plasma within the circulatory system. Normal values for man vary widely (Gregersen and Rawson, 1959); in young men total blood volume is about 77 ml./kg. with a standard deviation of about 10 per cent. (Gregersen and Nickerson, 1950). Major deviations from mean values are mainly due to differences in adiposity. It is better expressed in terms of lean body weight, a parameter more closely related to the active metabolic mass of the body (Allen *et al.*, 1956).

The circulation of the blood is fundamental in maintaining the constancy of the composition, volume and temperature of the interstitial fluid. All organs depend on it for the transport of oxygen and substrates for synthesis and energy transformations, and for the removal of the end-products of catabolism for excretion. Thus homeostasis is seriously deranged when a substantial amount of blood is lost by haemorrhage, the consequent reduction in blood flow and circulating blood volume having widespread effects which involve every organ of the body (Wiggers, 1950; Cuthbertson, 1960).

The effects of haemorrhage depend partly on the amount of blood lost, and partly on the rate of loss.

SLOW CHRONIC BLOOD LOSS

Slow chronic blood loss is tolerated better than rapid loss. The plasma volume expands so that the total blood volume is not greatly changed (Gibson, 1939). Red cell replacement is less able to keep pace with their loss than plasma replacement, although red cell production is increased so long as the body iron stores can be maintained. Their depletion exacerbates the characteristic anaemia and incomplete haemoglobinization of the red cells, resulting in a microcytic hypochromic iron-deficiency anaemia. The reduction in the oxygen capacity of the blood results in a state of anaemic hypoxaemia, which is compensated by an increase in cardiac output, appreciated clinically as a hyperdynamic circulation. Such patients are less able to withstand acute reduction of blood volume (and cardiac output) than normal subjects, for oxygen transport is lowered below body requirements by smaller reductions of cardiac output.

ACUTE HAEMORRHAGE

The immediate effects of rapid blood loss result from an acute lowering of the circulating blood volume. The most important effect is diminished cardiac output (Cournand *et al.*, 1943; Richards 1943–1944; Barcroft

et al., 1944). These changes initiate a wide variety of metabolic disturbances and mechanisms to support the circulation and replace the blood loss. The responses include central and sympathetic nervous activity, increased secretion of adrenaline, nor-adrenaline, adrenal glucocorticoids and mineralocorticoids, and posterior pituitary anti-diuretic hormone. Intestinal secretions and salivary flow are reduced. Urine formation diminishes or ceases. The coagulation time of the blood is considerably shortened.

The quantity of oxygen which is available to the body in unit time equals the product of cardiac output and arterial oxygen content (or cardiac output $\times$ arterial oxygen capacity $\times$ arterial oxygen saturation). For a normal man under resting conditions the total available oxygen (Richards, 1943–1944) is about 1,000 ml. STPD/min., roughly four times the basal oxygen requirements, corresponding to an arterio-venous oxygen saturation difference of about 25 per cent. Severe haemorrhage, by lowering cardiac output, reduces the available oxygen. The tissues extract more oxygen from each volume of blood, and the decrease in blood flow is reflected in severe desaturation of the venous blood. Barcroft (1920) described this state as stagnant anoxaemia. Despite the increase in extraction of oxygen, tissue oxygen tension is reduced but total oxygen consumption only falls when tissue perfusion becomes inadequate. The reactions to increasingly severe blood loss can be described in three stages: (1) depletion of venous reservoirs, (2) failure to maintain systemic blood pressure, (3) deterioration to death by vicious cycles.

1. Depletion of venous reservoirs

There is an optimal relationship between blood volume and the capacity of the vascular bed, for the circulatory system must be adequately distended with blood in order to maintain central venous pressure and venous return. Although the systemic blood pressure is governed by cardiac output and peripheral resistance, the changes in blood pressure produced by sympathetic activity are due, not only to changes of arteriolar resistance, but also to changes in the distensibility of the circulatory capacity. These occur mainly in the venules and veins, which accommodate 60–70 per cent. of the blood volume. Venoconstriction resulting in a 1–2 per cent. reduction of their capacity can roughly double diastolic inflow to the heart from one heart-beat to the next (Heymans and Neil, 1958). The main blood reservoirs comprise the cutaneous venous plexuses, the large veins, the splanchnic bed, the pulmonary vessels and the heart. Contraction of these reservoirs mediated by baroreceptor reflex and sympathetic activity can compensate for blood volume reductions of up to 10 per cent. without changes in cardiac output or blood pressure. Contraction of the spleen is only a minor factor in man, contributing about 50 ml. to the blood volume.

Circulatory changes appear when the blood volume reduction exceeds 10 per cent. Blood pressure is maintained by an increase in arteriolar constriction, due in part to reflex sympathetic activity, and in part to secretion of adrenaline and nor-adrenaline. A slight fall in central venous and right auricular pressure occurs (Warren *et al.*, 1945). Stroke volume falls, and the reduced pulse pressure results in lessened activity from the baroreceptors, atrial and ventricular receptors, causing reflex tachycardia as well as contributing to the prevailing state of vasoconstriction. This reflex vasoconstriction is selective, principally affecting splanchnic and limb vessels, especially those in the skin. The cutaneous vasoconstriction results in cooling of the skin, which probably evokes a hypothalamic response of increased vasoconstriction.

Further haemorrhage causes a progressive decline of cardiac output, while cardiac acceleration and vasoconstriction maintain the systemic blood pressure, which may fall slightly, remain unaltered, or even show a slight rise. Blood flow tends to be preserved through the brain and myocardium, circulations which are relatively independent of reflex vasoconstriction. Corticohypothalamic excitation reinforces the sympathetic activity; reduced baroreceptor discharge and increased chemoreceptor activity stimulate the mesencephalic reticulum, thus contributing to the signs of restlessness (Neil, 1962). This state is seen clinically as so-called " compensated shock " after reductions of blood volume up to about 20 per cent. (Grant and Reeve, 1951). Great individual variation exists in the extent to which a patient can compensate in this way. However, despite a normal blood pressure, tissue perfusion is considerably reduced.

2. Failure to maintain systemic blood pressure

Systemic blood pressure declines after 20–30 per cent. reductions in blood volume; after 45–50 per cent. reductions the blood pressure is frequently unmeasurable by clinical means (Grant and Reeve, 1951). Maintenance of the blood pressure depends on cardiac output and peripheral resistance. Both may fail as a result of haemorrhage.

A sudden fall in peripheral resistance due to dilatation of muscle arterioles occurs during venesection of conscious volunteers. It is accompanied by bradycardia and a profound fall in blood pressure, which results in fainting, presumably from cerebral ischaemia. A slight increase in the previously low cardiac output then occurs (Barcroft *et al.*, 1944). As much as 40 per cent. of the total blood volume can be removed from recumbent men in this way without fainting. This type of response is unusual in clinical practice, although a similar reaction is sometimes seen in man after injury complicated by moderate haemorrhage (Grant and Reeve, 1951).

Progressively greater exsanguination usually results in a fall of blood pressure associated with increasing tachycardia. Circulatory capacity can

no longer be reduced by vasoconstriction, and auricular and venous pressures fall as haemorrhage continues. Further reduction of cardiac output is usually ascribed to reduced venous return; it is only broadly related to the degree of oligaemia. Stroke output is further reduced. With the fall in blood pressure, reflex adjustments are intensified. The chemoreceptors of the carotid and aortic bodies are stimulated intensely by the stagnant hypoxia. Slow rhythmic variations in the systemic blood pressure known as Mayer waves (Mayer, 1876) may appear, which are mainly due to variations in chemoreceptor activity resulting from pressure-dependent flow changes through the carotid and aortic bodies (Åstrand *et al.*, 1958); they have also been observed in venous pressure records (Freeman and Graham, to be published).

Regional circulatory changes. The lowered mean arterial pressure head diminishes the perfusion pressure through all the tissues; the peripheral resistance increases as the flow through the various beds slows. The different beds are not affected equally. Flow through the *skin and muscle* is drastically curtailed, although flow to the intercostal muscles and diaphragm is relatively well maintained. Reduction of *renal blood flow* occurs while normal systemic pressures are maintained, the ensuing hypotension exacerbates the renal ischaemia (Lauson *et al.*, 1944). Renal oxygen consumption falls linearly with flow until glomerular filtration ceases, when it decreases exponentially (Kramer and Deetjen, 1960). The ischaemia may cause irreversible damage. The intense vasoconstriction of the *splanchnic area* and the consequent reduction in portal blood flow has a particularly deleterious effect on the liver, which receives most of its blood (and oxygen) from the portal vein, thus contributing to the failure of the liver to dissimilate lactate and other metabolites.

Blood flow is better maintained through the brain and myocardium than through other organs during haemorrhagic hypotension. *Cerebral blood flow* is maintained until the perfusion pressure drops below some critical level (Carlyle and Grayson, 1956; Lassen, 1959). The marked reduction of arterial P_{CO_2} due to hyperventilation may contribute to the reduction of cerebral blood flow to levels lower than can be ascribed to the hypotension alone. In severely bled man, intravenous morphine has been shown to cause a rise in arterial P_{CO_2} and a return of cerebral blood flow to normal, subjective improvement occurring without any change in blood pressure (Stone *et al.*, 1954). The cerebral ischaemic pressor response will intensify the systemic vasoconstriction. Despite a decline in vascular resistance, *coronary blood flow* is reduced, a result of the reduced aortic pressure and shortened diastolic intervals with tachycardia. The ECG in profound haemorrhagic hypotension shows the ST-segment changes characteristic of myocardial ischaemia.

Pulmonary blood flow is reduced *pari-passu* with cardiac output. Pulmonary-artery pressure declines with systemic blood pressure, tending to stabilize on reaching approximately half of the normal value. It probably fails to maintain blood flow through the upper parts of the lung, thereby increasing the number of unperfused alveoli and thus increasing physiological dead space.

Respiratory changes. Hyperventilation often occurs during rapid haemorrhage, associated with a temporary increase in arterial pH and decrease in arterial P_{CO_2} (Bjurstedt and Coleridge, 1962). This is chiefly chemoreflex in origin, with a small contribution from the baroreceptor mechanism. An increase in respiratory rate is sometimes accompanied by a reduction of tidal volume, little or no change occurring in the arterial P_{CO_2}. Thereafter an increasing degree of metabolic acidosis develops, due to the continuing stagnant hypoxia. It is accompanied by increasing alveolar hyperventilation, indicated by a progressive fall in arterial P_{CO_2} which tends to stabilize after an hour of haemorrhagic hypotension.

A great increase in the amount of dead-space ventilation occurs. This may reach 60–70 per cent. of the total ventilation from a normal of about 30 per cent. (Freeman and Nunn, 1963). The data of Cournand *et al.* (1943) confirm that physiological dead space is increased in patients during haemorrhagic hypotension. As a result of this, a great increase in total ventilation is necessary to maintain adequate alveolar ventilation and oxygenation of the arterial blood. This hyperventilation, which may be due in part to the metabolic acidosis, is clinically apparent as air hunger. The proportion of blood effectively shunted through parts of the lung with low ventilation/perfusion ratios does not increase, but the very low oxygen saturation of the venous blood enhances the reduction of arterial P_{O_2} resulting from the shunt (Freeman and Nunn, 1963).

Metabolic changes. The metabolic changes seen after haemorrhage depend not only on tissue hypoxia, but also upon endocrine and autonomic reactions. Variations in these responses may account for the differences between experimental findings, and observations made in clinical practice when haemorrhage is frequently complicated by tissue damage and infection. The changes continue into the period of recovery.

The stagnant hypoxia results in a metabolic acidosis, which becomes progressively worse as lactate, pyruvate and other fixed acids accumulate from tissue areas in which the P_{O_2} is reduced to the level at which anaerobic metabolism occurs. The acidosis is partly compensated for by the fall in arterial P_{CO_2} resulting from the hyperventilation.

Catabolism is increased. Carbohydrate metabolism is characterized by hyperglycogenolysis, resulting in hyperglycaemia and contributing to the increase in blood pyruvate and lactate. Its maintenance depends on the previous nutritional state of the individual; hypoglycaemia may result if the hypotension is prolonged. Protein catabolism is increased. At first the blood urea rises, later decreasing owing to diminished formation by the hypoxic liver. Blood non-protein nitrogen rises quickly, partly because of excessive protein breakdown and partly because of reduced deamination. Synthesis of peptides and proteins is also diminished, contributing to the decrease in plasma albumin; plasma fibrinogen and globulins (α_2 and γ) increase (Cuthbertson, 1960).

Recovery can occur after moderate haemorrhage. During and immediately after blood loss, the haemoglobin, haematocrit, red cell count and plasma protein concentration remain unchanged, but show a slight fall within two hours. This indicates addition of protein-free fluid, which results from the shift of interstitial fluid into the vascular space consequent upon decreased capillary hydrostatic pressure (Pappenheimer, 1953). Later, plasma proteins are added. The circulating volume is restored in approximately three days by an increase in plasma volume, resulting in anaemia. Thus the haematocrit continues to fall for 1–2 days after a rapid loss of 20–30 per cent. of blood volume (Moore, 1959). Final restoration of the red cell mass is slow, and is proportional to the amount of blood lost. It may take two months after haemorrhage of 500 ml., depending on the supply of iron.

Adequate blood transfusion therapy usually restores the circulation to normal. It also diminishes or cuts short some of the changes involving the distribution and excretion of electrolytes, as well as other metabolic effects (Flear and Clarke, 1955). Little retention of sodium or water occurs. Nitrogen excretion does rise in fully as well as undertransfused patients, but positive balance is more often achieved in transfused patients. After severe, prolonged haemorrhagic hypotension, however, transfusion may not reverse the metabolic acidosis.

3. Deterioration to death by vicious cycles

Provided that the systemic arterial hypotension is not too severe, the cardiovascular system and respiration can remain in a precarious state of equilibrium for several hours. But the functional state of the vital organs deteriorates with time, oxygen transport may become critical, and irreversible circulatory or respiratory failure may occur in several ways.

With the cardiovascular system balanced in a state of arterial hypotension and extreme vasoconstriction, any factor which depresses the blood pressure or increases circulatory capacity tends to initiate a vicious cycle, which leads to further disorganization of the regulatory mechanisms of arterial blood pressure and circulatory capacity (Heymans, 1950). Thus

failure of venomotor tone due to alcohol, anaesthesia, active warming of the skin or gravitation of blood into dependent limbs leads to dilatation of the venous bed and a profound decrease in venous return by blood pooling. The consequent reduction of cardiac output may then end in the available oxygen falling below basal requirements. Continued haemorrhage, with increasing tachycardia, may further reduce the already diminished coronary flow and venous return to such a degree as to end in cardiac arrest. Vasomotor centre ischaemia may result in loss of neural

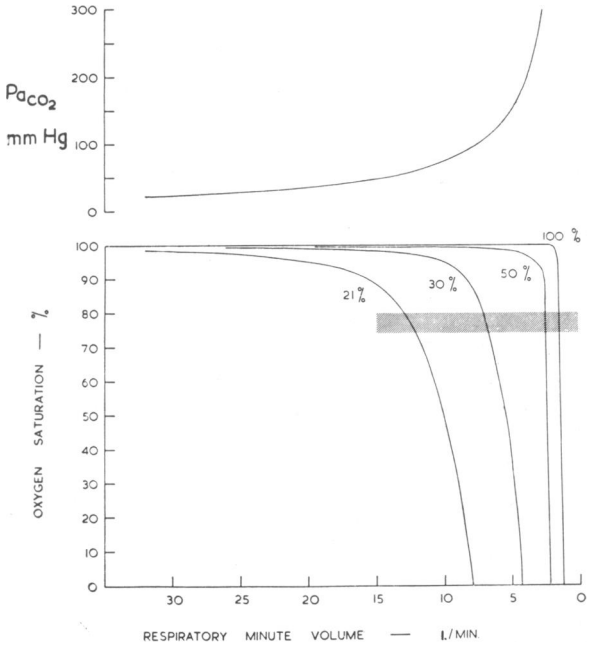

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Fig. 1. Data extrapolated from dog to man to indicate the likely relationships, after severe haemorrhage, between respiratory minute volume and arterial P_{CO_2} and oxygen saturation for different concentrations of oxygen in the inspired gas (in a steady state). Eighty per cent. saturation has tentatively been indicated as the lowest which would be compatible with life under these conditions (from Freeman and Nunn, 1963).

control, ending in relaxation of the constricted venous reservoirs and irregular oscillations of blood pressure prior to death.

Because of the increase in dead space ventilation after severe haemorrhage, any reduction of the hyperventilation causes a sudden decrease in arterial oxygen saturation (Fig. 1). Thus any reduction in the ability to maintain an increased ventilation causes hypoxia. If to the state of stagnant hypoxia is added the complication of reduced oxygen saturation of the arterial blood, the available oxygen will quickly fall below the quantity required by the body. Thus serious desaturation, sufficient to cause

central cyanosis, is not compatible with the survival of the severely bled patient (Freeman and Nunn, 1963). In this way, the development of airway obstruction, depression of the respiratory centre by anaesthetic or other drugs, increasing physiological dead space due to continuing fat embolization or shunting of severely desaturated venous blood through collapsed lung may each reduce arterial saturation to such a degree that either a lethal oxygen debt develops, or a vicious cycle centred on hypoxic medullary depression is started (Freeman and Nunn, to be published). Thus reduced cardiac output, increased dead-space ventilation and interference with respiration may combine to cause a lethal oxygen deficit.

CIRCULATORY FAILURE IRREVERSIBLE BY TRANSFUSION

Occasionally patients are found who do not respond to restoration of the circulatory volume by transfusion after a period of severe prolonged haemorrhagic hypotension. This condition is sometimes referred to as " irreversible shock ". This is not a problem in young patients when severe haemorrhage has complicated injury; adequate transfusion restores the circulation to normal, although the prolonged renal ischaemia may cause sufficient renal damage to end in renal insufficiency (Artz *et al.*, 1955). It occurs chiefly in old patients who occasionally remain hypotensive despite normal blood volume. They are often found to have a normal or elevated central venous pressure and a marked metabolic acidosis, associated with a fall in plasma sodium and a rise in plasma potassium (Smith and Moore, 1962). Reversal of the acidosis by administration of alkaline solutions sometimes results in a marked improvement. Continuing haemorrhage must be excluded (Prentice *et al.*, 1954; Davis *et al.*, 1961). Other factors in the maintenance of refractory hypotension include severe sepsis, myocardial failure, and complications of injury such as air and fat embolism, and pneumothorax.

Much experimental work has been done on bled animals in the investigation of " irreversible shock " (Wiggers, 1950; Symposium, 1962). Their illness, however, differs from that seen in man. Dogs, after a prolonged period of haemorrhagic hypotension followed by infusion of the withdrawn blood, die after an illness characterized by progressive circulatory failure and frequent development of a copious bloody diarrhoea. Necropsy reveals splanchnic congestion and striking hyperaemic swelling or haemorrhagic necrosis of the duodenal and jejunal mucosa; histology of such mucosa shows distension and packing of the capillaries with erythrocytes (Lillehei, 1957; Freeman, 1962). Various mechanisms related to the microcirculation have been suggested to account for this pathological state (Fine, 1958; Hershey, 1960).

However, certain studies emphasize that prolonged stagnant hypoxia

causes irreversible damage. The survival of dogs after haemorrhage, which is related to the duration and intensity of the hypotension induced by bleeding (Wiggers and Ingraham, 1946; Wiggers, 1950), has recently been shown to be determined by the development of a tissue oxygen deficit (Crowell, 1961). Moreover, since oxygen consumption after haemorrhage is determined by the available oxygen, there is an optimal haematocrit for maximum oxygen consumption because of the dual role of the haematocrit in determining the oxygen capacity of the blood and its viscosity; maximum resistance to haemorrhagic hypotension coincides with the haematocrit (42 per cent.) in the range of maximum oxygen transport (Crowell, Ford and Lewis, 1959). Myocardial function also deteriorates after prolonged hypotension in bled dogs (Wiggers, 1950). Cardiac output becomes progressively less responsive to increases in atrial pressure and, on restoration of blood volume, atrial pressures rise above normal; their lowering towards normal causes cardiac output to decline (Crowell and Guyton, 1962). Finally, a systolic peak of coronary blood flow appears during prolonged haemorrhagic hypotension, which might indicate flow through parts of the myocardium incontractile as a result of prolonged hypoxia (Gregg, 1962). Such results suggest that an element of cardiac failure may contribute to refractory hypotension.

OXYGEN ADMINISTRATION AFTER HAEMORRHAGE

Substitution of 100 per cent. oxygen for air (21 per cent. oxygen) as the inspired gas, by raising the alveolar Po_2 from about 100 mm. Hg to about 650 mm. Hg, dissolves only 2 ml. of oxygen per 100 ml. blood. Provision of this extra dissolved oxygen has been the basis for giving oxygen after haemorrhage (Barach, 1944), but because its clinical effect has seemed only marginal and because significant arterial desaturation is so seldom apparent, there have been few studies of the effect of oxygen administered after haemorrhage. But a consequence of the increased dead-space ventilation that occurs after haemorrhage is that any reduction of the hyperventilation causes increased hypoxic hypoxaemia. Such a condition is very sensitive to oxygen enrichment of the inspired gas (Campbell, 1960), which accounts for the beneficial effect of oxygen enrichment during anaesthesia sufficiently deep to depress the hyperventilation that occurs after severe haemorrhage (Freeman, 1962). The minimum safe respiratory minute volume is critical, but oxygen enrichment of the inspired gas lowers the tolerable level of ventilation (Fig. 1), the change from 21 per cent. to 30 per cent. oxygen being as effective as the change from 30 per cent. to 100 per cent. oxygen (Freeman and Nunn, 1963). Thus administration of oxygen after haemorrhage will prevent or eliminate arterial oxygen desaturation, and prevent or defer the vicious respiratory and circulatory cycles which end in death. In this way its value after severe haemorrhage may be more than marginal, and it should be administered

while arresting the bleeding and starting blood transfusion. Moreover, the oxygen may not have to be given in the high concentrations generally held to be essential (Annotation, 1963).

SUMMARY

Substantial haemorrhage deranges homeostasis, the consequent reduction in blood flow and blood volume having widespread circulatory, metabolic, endocrine and autonomic effects. The most important effect of decreased blood volume is diminished cardiac output, which reduces arterial oxygen transport resulting in a state of stagnant hypoxia and metabolic acidosis. A considerable increase in dead-space ventilation occurs. Further reduction of cardiac output and interference with the hyperventilation may combine to cause a lethal oxygen deficit; this may be exacerbated by complications resulting from injury. Prolonged renal vasoconstriction and consequent ischaemic renal damage may be sufficiently severe to cause renal insufficiency. Prolonged stagnant hypoxia may cause irreversible damage, and together with an element of cardiac failure may contribute to refractory hypotension. Oxygen administration after severe haemorrhage may prevent or defer the vicious respiratory and circulatory cycles which end in death.

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Question from Dr. J. P. Bull (Birmingham Accident Hospital)

Dr. Freeman has described a potentially important mechanism which might cause arterial desaturation following blood loss. How often has such desaturation been found in clinical cases? He quoted the findings of Cournand and Richards in support of the altered ventilation conditions, but the same investigators reported normal or near normal arterial oxygen saturation in the cases they studied. The same was true of the experimental haemorrhagic shock in dogs investigated by Wiggers.

Reply by Dr. J. Freeman

Very few clinical studies of arterial oxygenation after uncomplicated severe blood loss have been made in man. Significant arterial desaturation has not been reported. In the four cases of uncomplicated haemorrhage reported by Cournand *et al.* (1943) the mean arterial oxygen saturation was 95.9 per cent. (95.2–97.1 per cent.).

In clinical situations, however, haemorrhage is frequently complicated by injury, sedation or respiratory disease, and there are several reports of arterial desaturation in these circumstances. Thus the means and ranges of arterial saturations in patients reported by Cournand *et al.* were: normal controls, 96 per cent.; skeletal trauma with no shock, 94.2 per cent. (91–97.4 per cent.); skeletal trauma with mild shock, 90.8 per cent. (85.7–95 per cent.); skeletal trauma with moderately severe shock, 94.6 per cent. (83–99 per cent.); abdominal injuries with shock, 86.5 per cent. (72.8–94.8 per cent.). Significant desaturation has also been observed after

experimental haemorrhage, but in each instance blood loss was complicated by anaesthesia. Wigger (1950) observed the changes of arterial oxygen *content* after haemorrhage, and stated that the reduction of arterial oxygen was never great at the end of oligaemic shock. A diminution of arterial oxygen content occurred after bleeding in some of his dogs in which the haematocrit remained unchanged.

Marked arterial desaturation is incompatible with the survival of severely bled subjects because of the reduction of cardiac output. This may well account for the paucity of reports of central cyanosis after haemorrhage.

BLOOD VOLUME IN CHILDREN

by

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KNOWLEDGE OF A patient's blood volume is of value in clinical practice because a normal circulating blood volume is one of the prerequisites of a normal cardiac output. If blood volume is significantly reduced, cardiac output will fall, although compensatory mechanisms may minimize the degree of this fall; while an acute increase in blood volume (over-transfusion) may cause heart failure, especially in a diseased heart. Because of the relationship which exists between blood volume (considered as a static quantity) and circulatory performance, certain pertinent features of the circulation of the child will be discussed first.

CIRCULATION AND BLOOD VOLUME

At birth, the profound adjustments which occur when the circulation changes from a foetal to a neonatal design are associated with two important alterations in blood volume: (1) separation of the foetal or newborn circulation from the placental one; and (2) an increase in the size of the total vascular bed of the newborn when the lungs expand with the onset of breathing.

1. The role of placental blood

During or soon after normal delivery, whether *per vaginam* (Gunther, 1957) or by section (Secher and Karlberg, 1962), an average of about 80 ml. of blood is transferred from placenta to the newborn infant before pulsation of the cord ceases (even without " milking " of the cord), provided the placenta is held high enough above the child's body to provide a satisfactory head of pressure. This volume represents about 25 per cent. of an average infant's total blood volume (assuming such an infant to weigh 4 kg.). However, this sudden increase in blood volume is not accommo-